

Cortisol levels and prospective and retrospective memory in humans

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Abstract

OBJECTIVES: The aim of this study was to examine (i) the influence of cortisol on both prospective and retrospective memory performance and (ii) the role of emotional valence in both types of memory.

METHODS: Thirty-four male students participated in a memory task, which measured both prospective and retrospective memory performance. Baseline salivary cortisol levels were assessed.

RESULTS: Spearman's rank order correlation analysis showed a significant positive correlation between salivary cortisol levels and retrospective memory performance for neutral words. Cortisol levels were not significantly correlated with prospective memory performance for either negative nor neutral words.

CONCLUSIONS: The present results indicate chronic cortisol levels are positively associated with retrospective memory at relatively low concentration ranges, but not prospective memory, in healthy young men. Implications for evaluating the beneficial effects of low-dose cortisol treatment on posttraumatic stress disorder is discussed.

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Introduction

Stress hormones have been shown to modulate various types of neural activities [15]. Although memory processing has been associated with both baseline and acutely elevated stress hormone levels [3, 9, 15], most previous studies have not paid attention to type of memory.

Over the course of an average day we are required to both remember the details of past experiences (i.e., retrospective memory) and realize intentions that must be delayed for some period of time while engaged in other activities

(i.e., prospective memory [5]). Although the relationship between stress and retrospective memory (e.g., the recognition of previously learned spatial and/or verbal material) has been extensively studied, little is known regarding how affective factors modulate prospective memory. Prospective memory has been found to be impaired in normally aging adults [4] and healthy young participants with high anxiety [6]. Neuroimaging studies have shown that the prefrontal cortices and/or the anterior cingulate are activated when

people perform a prospective memory task [2,8]. As far as we know, there are no studies examining the relationship between the level of stress hormones and prospective memory.

Several studies have shown that cortisol (a stress hormone in humans) may influence various types of retrospective memory, such as social memory [14], spatial memory [3,9], and emotional verbal memory [16] via GRs (glucocorticoid receptors) and MRs (mineralocorticoid receptors) in the hippocampus and the amygdala. In rodent animal studies, it has been found that activation of GRs, induced by high levels of corticosterone (a stress hormone in rodents) in the hippocampus, reduces non-emotional retrospective memory. On the other hand, the activation of MRs, induced by low levels of corticosterone, has been found to enhance retrospective memory [3,9]. To date, it has not been clearly demonstrated that cortisol levels at low concentration ranges are positively correlated with neutral retrospective memory in humans.

It has also been reported that emotional retrospective memory is more vulnerable to elevated cortisol than non-emotional retrospective memory [7], which may result from β -adrenergic pathway-dependent GR activation in the amygdala [11]. However, it appears no study to date has examined the impact of cortisol levels on neutral and emotional prospective memory.

The aim of this study was to demonstrate the relationship between cortisol levels and both non-emotional (neutral) and emotional (negative) prospective/retrospective memory in humans. Results have important implications for evaluating the beneficial effects of low-dose cortisol treatment on 're-experience' and 'intrusions' in patients with posttraumatic stress disorder [1].

Materials and methods

Participants:

A total of 34 male undergraduate students from Hokkaido University participated in this study. The mean age was 19.0 years (range 18–21). Smokers, drinkers, and participants taking medication, or suffering from acute or chronic hormonal dysregulations, atopic-, psychosomatic, or psychiatric diseases were excluded. To avoid the effects of a menstrual hormonal cycle, only male participants were selected. Participants were informed that the study involved investigating the relationship between neuroendocrine measures and cognitive performance. They were given instructions not to drink anything containing alcohol or caffeine from 8:00 p.m. on the day prior to the experiment, and not to eat nor drink anything except water, nor do physical exercises within one hour prior to their participating in the experiment.

Procedure:

Individual differences in circadian hormone rhythms were minimized by conducting all sessions between 1445 and 1745 hours. Participants were tested individually. On arrival, participants rested for two minutes.

The experimenter then collected a saliva sample from the participants. This was followed by the memory task. Saliva was collected from the participants using Salivette (Sarstedt, Rommelsdorf, Germany) collection devices. Saliva samples were immediately frozen and stored at -20°C until a biochemical analysis was conducted. Before assaying the saliva samples for cortisol, they were thawed and centrifuged. This results in low viscosity saliva. Cortisol in saliva was determined using an enzyme-linked immunoassay method employing a polyclonal anti-cortisol antibody [12,13,14]. All procedures determining salivary cortisol levels were conducted using the standard protocols by Teikoku Hormone Medical Co. Ltd. (Japan), which has extensive experience in various steroid hormonal assays [12,13,14]. Staff at the company did not know the nature of the experimental conditions.

Memory task:

In a laboratory experiment, prospective memory is usually measured by whether individuals remember to perform an intended action at some later time [5]. Although many of these tasks can only measure prospective memory, a procedure used by Harris and Menzies [6] can measure both prospective and retrospective memory [6]. Based on this procedure, we created a memory task that measured both prospective and retrospective memory, and which included both neutral and emotional words. In this task, a list of 60 words was constructed. All the words were Japanese nouns. Half of the words were negative, while the other half were neutral. The words were selected from the results of a panel of 11 'judges' who were asked to rate the negative and positive valence for each word (1: most negative to 7: most positive). The average score for negative words was 1.68 (range: 1.13–2.40); while for neutral words it was 4.20 (range: 3.80–5.50). A total of eight targets, for testing prospective memory, were embedded within the word list. Four target words were negative, and consisted of a name of a physical disorder (i.e. dizziness, stiff neck, numbness, and headache); four target words were neutral and consisted words for articles of clothing (i.e. suit, uniform, socks, and 'yukata' – a light cotton kimono). The target words were the only words included in the list from both categories.

All instructions were provided on a computer display. Participants were instructed to think of an association and write down that association on the sheet in front of them after the word was displayed (distracter task). They could write down only one word. For example, if the word displayed on computer was 'zoo', they could write down 'lion', 'monkey', 'cage' or such similar words. Participants were told they would be asked to remember the displayed words later. In order to test their prospective memory performance, they were also told that whenever a displayed word could be classified as a piece of clothing (e.g. sweater) or as a name of disorder (e.g. nausea), they had to place a cross next to the associated word on the sheet.

The words were displayed at a rate of one word every four seconds. After displaying all 60 words, retrospective memory was tested in a free recall task. For the free recall task, participants had to recall as many of the displayed words as possible within a five minute period. Following the free recall test, participants were asked to indicate on their response sheets if they had any difficulties in understanding the instructions. Memory performance was defined as the percentage of correct answers [6] – namely, [retrospective memory performance] = $100 \times [\text{number of correctly recalled words in the free recall task}] / 60$, and [retrospective memory performance] = $100 \times [\text{number of correctly checked targets}] / 8$.

Statistical analysis: All statistical analyses were conducted using the software R Version 2.1.0 [10]. Because of distortions in the shape of distributions of cortisol concentration and prospective memory scores, Spearman's rank correlations were used. Significance level was set at 5% throughout.

Results

Descriptive statistics: The average baseline cortisol level of the participants was 4.55 ± 3.41 nmol/l ($n = 34$). Participants' performance for prospective and retrospective memory tasks, which was similar to values in a previous study [6], is summarized in Table 1.

Relationships between cortisol levels and memory performance: For retrospective memory, baseline cortisol levels were significantly positively correlated with

Table 1: Mean and standard error (SE) of memory performance ($N = 34$)

Prospective memory	69.9 ± 5.3
neutral words	69.9 ± 5.8
negative words	69.9 ± 5.8
Retrospective memory	30.9 ± 1.3
neutral words	32.7 ± 1.9
negative words	29.1 ± 1.7

Note that memory performance is defined as the percentage of correct answers.

neutral retrospective memory performance ($r_s = .35$, $p < .05$; see Fig. 1), indicating that MRs in the hippocampus may have predominantly been activated by cortisol in participants. In contrast, baseline cortisol levels were not significantly correlated with negative retrospective memory performance ($r_s = .17$, ns), implying that hippocampal MR's memory-enhancing actions were not strong for negative retrospective memory. With respect to prospective memory, neither negative nor neutral prospective memory performance was significantly correlated with baseline cortisol levels ($r_s = .13$, ns, and $r_s = .09$, ns, respectively), indicating that cortisol may not have dramatically impacted neural processing underlying prospective memory.

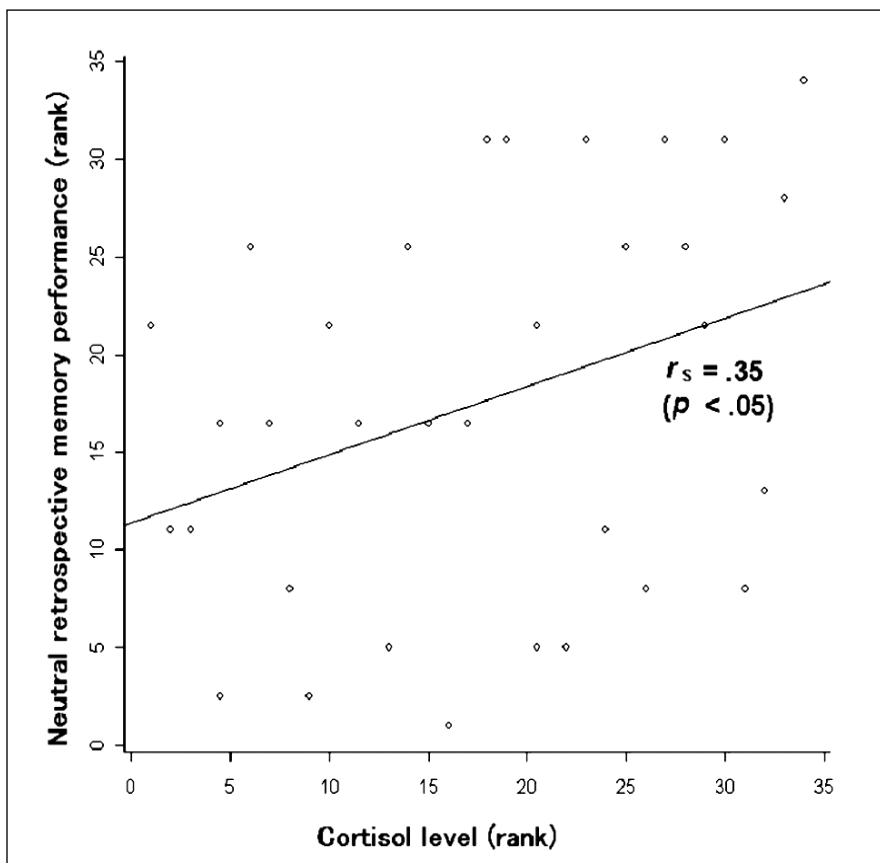


Figure 1. Scatterplot of baseline cortisol levels and retrospective memory performance for neutral words. A significant positive correlation was observed ($r_s = 0.35$, $p < 0.05$, $N = 34$).

Discussion

This study is the first to examine the relationship between baseline cortisol levels and prospective and retrospective memory for neutral and negative words. Our results suggest that: (i) baseline cortisol levels are positively associated with retrospective memory for neutral words, but not with retrospective memory for negative words; and (ii) both neutral and negative prospective memory do not appear to be sensitive to baseline cortisol levels.

Research utilizing a rodent animal model, has shown that stress hormones may have biphasic actions on hippocampus-dependent memory performance [3,9,15]. In other words, within a low concentration range, a stress hormone enhances retrospective memory for neutral materials (e.g. spatial memory) via MR activation in the hippocampus; while at a high concentration range, a stress hormone impairs memory performance via GR activation [3,9]. Consistent with this finding, our study demonstrated that baseline cortisol levels were positively associated with retrospective memory for neutral words at relatively low concentration ranges. (Please note, participants were not exposed to a laboratory stressor in the present study).

The question needs to be asked – why was a significant relationship observed for neutral but not negative words in the present retrospective memory task. Recently, it has been reported that human retrospective memory for emotional words are more likely to be significantly impaired by GR activation induced by social stress-induced cortisol elevation in the amygdala [7]. Therefore, it is possible that in the present study, the cortisol's memory-enhancing effect via MR activation in the hippocampus on negative emotional memory was diminished by cortisol's memory-impairing actions via GR activation in the amygdala. These findings imply that recently proposed low-dose cortisol treatment on mood disorders in patients with posttraumatic stress disorder may facilitate neutral retrospective memory without enhancing remembering previous negative events [1]. It is possible that other more emotionally-arousing negative materials, than the words used in this study, may significantly impact retrospective memory. However, it is also possible that emotional valence for negative stimuli may be dependent on direct personal experience and therefore difficult to standardize. This should be examined in future studies.

With respect to prospective memory for neutral and emotional words, neither GR- nor MR-dependent neuronal pathways appear to significantly account for participants' memory performance, suggesting that these stress hormone receptors are not strongly involved in neural activities underlying neutral or emotional prospective memory in brain regions such as the prefrontal cortices, the anterior cingulate, and the amygdala. Therefore, our results suggest that low-dose cortisol treatment for mood disorders [1] may not impair prospective memory, which is important for everyday life, also supporting the beneficial effect of low-dose cortisol treatment.

There are two major limitations of the present study. First, in order to examine whether emotional valences affect the relationship between cortisol levels and prospective and retrospective memory, positive words should be included in the memory task in future studies. Second, because it has been reported that stress hormones' impact on memory differs between the sexes [17], future studies need to include female participants.

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